

Partial breast radiotherapy after breast conservation surgery for early breast cancer: 5-year outcomes from the IMPORT LOW (CRUK/06/003) phase III randomised controlled trial

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Abstract

Background:

Local cancer relapse rates after breast conservation surgery followed by radiotherapy have fallen sharply in many countries with risk influenced by patient age and clinico-pathological factors. In women at lower than average risk of local relapse, partial breast radiotherapy restricted to the vicinity of the original tumour is hypothesised to improve the balance of beneficial versus adverse effects compared with whole breast radiotherapy.

Methods:

The IMPORT LOW trial (ISRCTN12852634) recruited women aged ≥ 50 years after breast conserving surgery for invasive ductal adenocarcinoma $pT \leq 3\text{cm}$, $pN0-1$, G1-3 and $\geq 2\text{mm}$ resection margins. Using 15 daily treatments, patients were randomly allocated (1:1:1) to 40 Gy whole breast radiotherapy (control), 36 Gy whole breast plus 40 Gy to partial breast (reduced dose) or 40 Gy partial breast only (partial breast). Primary endpoint was ipsilateral local tumour control (80% power to exclude a +2.5% non-inferiority margin at 5 years for each test group). Field-in-field intensity modulated radiotherapy was delivered using standard tangential beams that were simply reduced in length for the partial breast group.

Findings:

Between May 2007 and October 2010, 2018 women were recruited (control $n=675$, reduced dose: $n=674$, partial breast: $n=669$). With a 72.2 month median follow-up (IQR 61.7-83.2), 5-year local relapse rates were 1.1% (95%CI 0.5-2.3), 0.2% (0.02-1.2) and 0.5% (0.2-1.4) in control, reduced dose and partial breast groups. Estimated absolute differences in local relapse rate compared with the control group were -0.73% (-0.99, 0.22) for the reduced dose and -0.38% (-0.84, 0.90) for the partial breast groups, demonstrating non-inferiority for both test schedules. Photographic, patient and clinical assessments recorded comparable, and in some domains, lower, levels of adverse effects after reduced dose or partial breast radiotherapy, including two patient domains achieving statistically significantly lower adverse effects compared with whole breast radiotherapy. Breast cancer prognosis was excellent with no statistically significant difference in rates of distant relapse, disease-free survival and overall survival between treatment groups.

Interpretation:

At 5 years, partial breast and reduced dose radiotherapy achieved local relapse rates non-inferior to those observed following whole breast radiotherapy in selected patients with early

breast cancer and equivalent or milder late normal tissue adverse effects. This simple radiotherapy technique is implementable in radiotherapy centres worldwide.

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Manuscript

Introduction

Breast radiotherapy after breast conserving surgery has been shown to reduce the risk of any recurrence by one-half and breast cancer mortality by one-sixth in patients with early breast cancer [1]. Whole breast radiotherapy is standard of care in the UK and internationally [2-5]. Current treatment guidelines discuss partial breast radiotherapy in selected patients based mainly on retrospective and prospective cohort studies after treatment using Mammosite® and by mature results of a single relatively small well-conducted randomised trial of interstitial brachytherapy [6-10].

One challenge in treating women with early breast cancer has always been to reduce the morbidity of radiotherapy without compromising cure. The rationale for investigating partial breast radiotherapy is based on falling local relapse rates reported internationally, and recognition that a majority of ipsilateral local relapses occur close to the region of the index tumour, the so-called tumour bed [11, 12]. Rapid technical advances in radiotherapy combined with accurate localisation of the tumour bed using titanium surgical clips enable more precise matching of radiotherapy dose intensity to the spatial variation in local relapse risk. This can now be achieved using a linear accelerator [13-15]. The advantages of this approach are predicted to be fewer chronic adverse effects given the lower exposure of organs at risk, including breast tissue, ribcage, lung and heart, without loss of local tumour control. Many thousands of patients are currently under follow-up in randomised studies, but mature (5 years or more) data are available for a minority [7, 16-18]. Against this background, we report 5-year results of the first phase III trial testing partial breast radiotherapy using a standard external beam technique and delivered after complete local tumour excision of low risk early breast cancer.

Methods

Study design

IMPORT LOW is a multicentre randomised phase III non-inferiority trial comparing the safety and efficacy of standard whole breast radiotherapy using accelerated schedules of 40 Gray (Gy) in 15 fractions (f) (control) with two experimental schedules of 36 Gy/15f to the whole breast and 40 Gy/15f to the partial breast (reduced dose), and 40 Gy/15f to the partial breast only (partial breast) [19]. All treatment groups received simple forward-planned intensity-modulated radiation

techniques (IMRT) to optimise dose homogeneity. There were two substudies addressing late adverse effects, including photographic assessments of the breast and comprehensive patient reported outcomes; centres declared upfront whether they wished to participate in the substudies. Within participating centres, all patients approached about IMPORT LOW were informed about the substudies, and separate consent was given to main trial and substudies. Patients were recruited from the participating sites until planned substudy sample size had been obtained.

Participants

Women who were aged 50 years or older who had breast conserving surgery for unifocal invasive adenocarcinoma (excluding invasive carcinoma of classical lobular type), pathological tumour size ≤ 3 cm (pT1-2), axillary node negative or 1-3 positive nodes (pN0-1), any grade and with minimum microscopic margins of ≥ 2 mm were eligible. Patients were ineligible if they had a previous malignancy of any kind (unless non-melanomatous skin cancer), had undergone mastectomy, received neoadjuvant chemotherapy or concurrent adjuvant chemo-radiotherapy. Primary endocrine therapy was allowed as long as the tumour was less than 3.0cm, all other inclusion criteria were met and surgery was carried out. Eligibility criteria were amended twice during the trial. Women with grade 3 tumours and/or tumours > 2 cm were excluded prior to a protocol amendment (approved 04/03/2008). A subsequent amendment (approved 07/05/2009) allowed inclusion of lymphovascular invasion and patients with 1-3 positive nodes. Falling local relapse rates demonstrated within the START trial and other studies, indicated that it was safe to broaden the eligibility criteria¹¹. The study was approved by the Oxfordshire Research Ethics Committee B (06/Q1605/128). It was sponsored by The Institute of Cancer Research and was conducted in accordance with the principles of Good Clinical Practice. All patients provided written informed consent. The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) were responsible for study management and carried out central statistical data monitoring and all analyses. The Trial Management Group was responsible for day to day running of the trial and was overseen by an Independent Trial Steering Committee (TSC) and interim data reviewed confidentially by an Independent Data Monitoring Committee (IDMC). Patient advocates were involved at every stage of the trial, from initial study design through to preparation of the final manuscript.

Randomisation and masking

Women were randomly assigned (in a 1:1:1 ratio) to receive conventional whole breast radiotherapy or one of the two experimental schedules (reduced dose or partial breast). To randomise a patient, centres telephoned ICR-CTSU. Computer-generated random permuted blocks (mixed size 6 and 9) were used to stratify patients by radiotherapy treatment centre. Treatment allocation was not masked from patients or clinicians.

Procedures

It was strongly recommended to insert surgical clips, but if this was not possible, localisation of the tumour bed was achieved using ultrasound, MR or CT imaging [13, 20]. If it was not possible to adopt one of the recommended procedures, it was permissible to enter a patient provided the clinician was confident that clinical localisation was accurate, for example, if there was an obvious palpable tissue deficit (appendix 1). [13, 20] The protocol specified forward-planned field-in-field IMRT delivered by standard medial and lateral tangential beams reduced in length but not in width. Non-target breast tissue medial and/or lateral to the planning target volume was thereby included in the high dose zone (figure 1 for radiotherapy technique for partial breast group). Details of contouring and planning are described in the IMPORT LOW Radiotherapy Planning Pack (appendix 1), which was used in addition to the clinical protocol (appendix 2) and developed in partnership with the UK Radiotherapy Trials Quality Assurance (RTTQA) team. Each centre completed an initial questionnaire to establish details of their intended technique. In addition, the RTTQA team visited each radiotherapy centre before opening to validate independently the technique in use against the information given in the questionnaire. Measurements were made across the treatment volume within a purpose-made breast phantom, with particular reference to dose homogeneity. All plans together with corresponding computed tomography data sets were collected electronically and stored at the RTTQA repository. In addition, a subset of approximately 1 in 10 patients identified at randomisation had thermoluminescence dosimetry (TLD) measurements, which were also sent to the RTTQA team.

After radiotherapy, patients were scheduled for annual follow up to 10 years. Mammographic schedule was according to local practice, which was typically annually for the first 5 years and then 3-yearly as part of the national screening programme. Normal tissue effects were assessed by clinicians, patients and using photographs. Clinicians assessed breast shrinkage, distortion, induration, breast oedema and telangiectasia at 1, 2, 5 and 10 years using a 4-point scale (“not at all”, “a little”, “quite a bit” or “very much”), comparing the ipsilateral versus contralateral breast where relevant [21]. The year 1 assessment was only required after protocol amendment (approved 04/03/2008). Photographs were taken at baseline (post-surgery and pre-radiotherapy), 2 and 5 years for patients in the photographic substudy [22]. Patients in the patient reported outcomes substudy completed the EORTC QLQ-C30 core questionnaire, EORTC QLQ-BR23 breast cancer module, Body Image Scale, protocol-specific questions (skin appearance changed, overall breast appearance changed, breast smaller, breast harder/firmer to touch), Hospital Anxiety and Depression Scale and the EuroQoL EQ-5D-3L. These were scheduled at baseline (before randomisation), 6 months, 1, 2 and 5 years. Cases of symptomatic rib fracture, symptomatic lung fibrosis and ischaemic heart disease were recorded at annual follow-up.

Outcomes

The primary outcome measure was local tumour control, defined as the absence of *any* invasive/non-invasive carcinoma in *any location* in the ipsilateral breast parenchyma or overlying skin. This was recorded as “local relapse”. Secondary efficacy outcomes were location of local tumour relapse, time to regional relapse (axilla, supraclavicular fossa and internal mammary chain), time to distant relapse, disease-free survival (with an event defined as any local, regional or distant relapse, contralateral breast cancer or death due to breast cancer), overall survival, contralateral breast cancers and other second primary cancers. Secondary outcomes relating to late onset normal tissue effects were assessed by patients, photographs and clinicians.

Patient-reported outcomes focused on key items (arm/shoulder and breast) from the BR23 module and protocol-specific questions that were dichotomised as moderate/marked (“quite a bit/very much”) and presented as proportion occurring at five years and time to development of first moderate/marked event. Cross-sectional and time-to-event analyses characterise the pattern of normal tissue effects over time. This manuscript reports on selected items from the BR23 breast cancer module and protocol-specific questions that correspond to clinician-reported assessments. Further analysis of patient reported outcomes will be reported in a separate manuscript.

Digital photographs were scored as showing none, mild or marked change in breast appearance at 2 and 5 years compared with baseline by 3 observers using a previously described and validated consensus method [22]. Observers were blind to treatment allocation but not year of follow-up. Clinician-reported late normal tissue effects were also summarised as the proportion of patients with moderate/marked (“quite a bit/very much”) events at five years and time to development of first moderate/marked event, for each item scored.

Statistical analysis

The trial was powered to evaluate non-inferiority of the local relapse rate for each of the experimental groups compared with the control group. A 2.5% local relapse rate at 5 years was assumed with whole breast radiotherapy and the trial aimed to exclude an increase of greater than 2.5% in local relapse rate in either experimental group. This required 645 patients in each group to give 80% power with alpha of 2.5% (one-sided) and allowing for 5% loss to follow-up by 5 years. A target number of events was not stated in the protocol but data maturity was reviewed and discussed by the IDMC and TSC. The IDMC considered data to be sufficiently mature once form return rates were at least 80% at 5 years.

The photographic substudy required 400 patients per group to have >90% power to detect at least a 10% difference in change in overall breast appearance for each experimental group compared with control (two-sided alpha of 0.025). With 400 patients per group, the patient reported outcome substudy had >80% power to detect differences of at least 15% in the prevalence of normal tissue effects (two-sided alpha of 0.005 to allow for multiple testing) and allowing for 10% attrition (due to death or illness). The same 0.005 threshold for significance was used for the clinician reported normal tissue effects.

Survival analysis methods were used to compare efficacy outcomes between the control group and experimental schedules with time measured from randomisation. For time to local relapse, patients were censored at death or at last follow-up for those who remained event-free. For distant relapse, disease-free and overall survival, patients not experiencing an event were censored at last follow-up. Nelson-Aalen cumulative hazard functions were plotted by treatment group.

Kaplan-Meier methods were used to estimate event rates at 5 years with 95% confidence intervals (CI). Estimates of treatment effect were made using unadjusted Cox regression models, with hazard ratios (HR) <1 indicating a decreased risk of the event in the experimental group compared with the control group. Absolute treatment differences in local relapse rate were calculated based on the Kaplan Meier estimate of the local relapse-free rate in the control group and the HR. Each experimental group could be considered non-inferior to the control group if the upper limit of the two-sided 95% CI for local relapse HR was <2.03 (critical hazard ratio, excluding an increase in local relapse from 2.5% to 5%). Superiority of each experimental group compared to the control could be tested if non-inferiority could be claimed (using a 0.025 significance level). Analyses were by intention to treat since compliance to allocated treatment was high. The primary outcome was also analysed in the per-protocol population, including all patients who completed their protocol-defined radiotherapy regimen, given this was a non-inferiority trial.

The proportion of late moderate/marked events at five years is reported for each clinician and patient-reported late normal tissue event. Fisher's Exact tests were used to compare each experimental schedule with the control group. Time to first moderate/marked event was analysed using the Kaplan-Meier method. Patients not experiencing an event were censored at last assessment of normal tissues (by clinician or patient as appropriate) or death. For the patient reported outcomes, the Cox model was adjusted for baseline scores. Photographic data is presented as the proportion of patients with none or mild/marked change in breast appearance at 2 and 5 years compared with baseline. The Fisher's Exact test was used to

compare each experimental schedule with the control group at both time points. There was no imputation of missing normal tissue data.

For all time-to-event analyses the proportional hazards assumption of the Cox model was tested using Schoenfeld residuals and found to hold. Analyses were based on a database snapshot taken on 15th June 2016, and performed using STATA version 13. This study is registered, number ISRCTN12852634.

Role of funding source

Cancer Research UK provided peer-reviewed approval for the trial but had no other role in study design, collection, analysis, interpretation of data, or report writing. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication. CG and JMB also had full access to study data.

Results

Between May 2007 and October 2010 2018 patients entered the study from 30 UK radiotherapy centres (control n=675, reduced dose n=674 and partial breast n=669). Four patients were found to be ineligible after randomisation (three patients had lobular carcinoma and one had previous renal cell carcinoma) and two patients withdrew consent from any data being used in analysis (Figure 2). Seven patients did not receive any radiotherapy and 54 did not receive their allocated treatment (Figure 2). Seventy-four percent of patients had surgical clips, 24% used imaging (either CT or ultrasound) and 2% used clinical methods alone to localise the tumour bed. Demographic and clinical characteristics were well balanced across the three treatment groups (Table 1). Chemotherapy was given to 104 (5%) women, 90% (n=1826/2008) had endocrine therapy and 2% (n=36/2008) had trastuzumab.

After a median follow-up of 72.2 (IQR 61.7-83.2) months, local relapse had been reported for 18 patients whole breast (n=9), reduced dose (n=3) and partial breast (n=6) groups respectively. At five years, the local relapse rates were 1.1% (95%CI 0.5-2.3) in those allocated to whole breast, 0.2% (0.02-1.2) in the reduced dose and 0.5% (0.2-1.4) in the partial breast groups respectively. The estimated absolute treatment differences in the local relapse rate compared with whole breast radiotherapy at five years was -0.73 (-0.99, 0.22)% for the reduced dose group and -0.38 (-0.84, 0.90)% for the partial breast group. Since the upper limit of the two-sided 95% confidence interval ruled out a >2.5% increase in local relapse risk for each of the test schedules, non-inferiority can be claimed for both reduced and partial breast radiotherapy. Confirmation of this assertion is illustrated by a test against the critical hazard ratio $HR > 2.03$, with $p=0.003$ and $p=0.016$ for the reduced and partial groups respectively compared with the whole breast radiotherapy group (Table 2 and Figure 3). Analyses in the per-protocol population were

consistent ($p=0.003$ and $p=0.017$ for the reduced dose and partial breast comparisons respectively). Local relapses occurred most frequently in patients with at least one high risk feature (Appendix 3).

Four regional relapses were reported: (whole breast ($n=1$), reduced dose ($n=1$) and partial breast ($n=2$) groups respectively, of which 2 coincided with local relapse and 2 were isolated axillary relapses. Rates of distant relapse, disease-free survival and overall survival were similar across treatment groups, with low overall event rates and no statistically significant differences observed between experimental and control groups. Thirty-two patients developed invasive contralateral breast primary cancers (whole breast ($n=10$), reduced dose ($n=11$) and partial breast ($n=11$) groups). Non-breast second primary cancers were reported for 96 patients (whole breast ($n=35$), reduced dose ($n=37$) and partial breast ($n=24$) groups (Table 3)). Gastrointestinal, gynaecological and lung cancers were the most common. All but one (18/19) of the lung cancers developed within five years of randomisation and there were similar numbers ipsilateral and contralateral to the treated breast (Appendix 4).

A total of 116 patients had died, 26 from breast cancer, 90 from other causes (including 42 from second cancers and 9 cardiac-related) and 2 with unknown cause of death with no evidence of disease relapse prior to death (Table 3). There were similar numbers of cardiac deaths for patients with left and right sided breast cancers (Appendix 5).

In relation to normal tissue effects, at the 5-year assessment, patients generally reported fewer moderate/marked events for the protocol-specific questions (skin change, overall breast appearance change, breast smaller and harder/firmer to touch) in the partial breast group compared with the whole breast group (Table 4), although this reduction was statistically significant for change in breast appearance only ($p<0.001$). Five-year cumulative incidence estimates indicated that change in breast appearance was the most common item reported as moderate/marked by patients. There was evidence of a significant reduction in moderate/marked events up to 5 years for both the reduced dose and partial breast ($HR<1$) compared with the whole breast group for breast harder/firmer only (reduced dose $p=0.002$; partial breast $p<0.0001$). Cumulative incidence rates of breast harder/firmer were much higher than the point prevalence at 5 years as they included events reported earlier on in follow-up, many of which were likely to be temporary post-surgical effects. The proportion of patients reporting arm and shoulder symptoms as moderate/marked at 5 years was low across all groups with no evidence of a difference for either experimental schedule compared with the control group. Similarly, cumulative incidence estimates indicated similar rates of arm and shoulder symptoms between groups

A total of 1319 women consented to the photographic substudy and baseline photographs were received and assessable for 1222 patients. Two year photographs were assessable in 1000 women. The most common reasons for photographs not being available were centre administrative oversight meaning photographic appointments were not made, patients not attending hospital visits and patients withdrawing consent from the substudy. At two years, mild or marked changes in breast appearance were observed in 37/332 (11%), 32/335 (10%) and 31/333 (10%) allocated to whole breast, reduced dose and partial breast radiotherapy respectively. At 5 years, photographs were available for 805 women and, compared with the 2-year results, the proportion of patients with mild or marked changes had increased across all groups (whole breast $n=60/262$ (23%), reduced dose $n=59/264$ (22%) and partial breast $n=50/279$ (18%)). There was no evidence of a statistically significant difference in the proportion of patients experiencing change in breast appearance for either experimental schedule compared with whole breast radiotherapy at 2 (reduced dose $p=0.527$; partial breast $p=0.446$) or 5 years (reduced dose $p=0.917$; partial breast $p=0.165$).

Clinical assessment of late normal tissue effects at 5 years showed very low levels of moderate/marked events across all treatment groups (Table 5). Breast shrinkage had the highest prevalence of moderate/marked events (whole breast $n=41/452$ (9%), reduced dose $n=37/478$ (8%) and partial breast $n=33/472$ (7%)). Moderate/marked breast oedema was rare at 5 years (whole breast $n=4/446$; reduced dose $n=2/468$; partial breast $n=0/468$). The cumulative incidences also indicated breast shrinkage to be the most common late normal tissue effect.. The hazard ratios for all late effects were consistently <1 but there was no evidence of statistically significant differences for individual events. Severe late adverse effects were rare. There were 4, 8 and 5 confirmed reports of rib fracture, lung fibrosis and ischaemic heart disease respectively (Appendix 6).

Discussion

Our 5 year results confirm that local relapse rates were very low across all trial groups and that non-inferiority was demonstrated for both partial breast and reduced dose radiotherapy. Late normal tissue effects were also uncommon across all groups and statistically significantly fewer in patient reported breast hardness in the partial breast radiotherapy group compared with control. This supports our hypothesis that partial breast radiotherapy using a standard radiation technique can reduce late toxicity without jeopardising local tumour control.

IMPORT LOW has several novel aspects. Firstly, it is the only phase III trial of partial breast radiotherapy to use the same dose-fractionation regimen and radiation technique in both whole breast and partial breast radiotherapy group(s). Therefore, differences in treatment outcome can be attributed more reliably to differences in radiotherapy volume. The Danish Breast Cancer

Group phase II partial breast radiotherapy trial is similarly designed to have breast volume as the only variable, but has a primary endpoint of grade ≥ 2 breast induration at 3 years (personal communication, B Offersen)

Other phase III partial breast radiotherapy trials report a variety of different dose-fractionation regimens ranging from a single intraoperative dose to 1-2 weeks of treatment [18, 23, 24]. These differences make it challenging to distinguish variations in outcome being due to differences in treated volume or to radiation dose-time effects. This is illustrated by the interim results at 3 years from the RAPID trial that compared 3D conformal partial breast radiotherapy using 38.5 Gy in 10 fractions over 5 days, with whole breast radiotherapy using 42.5 Gy or 50 Gy in 16 or 15 fractions respectively with an optional boost. Cosmetic outcome and late normal tissue toxicity were worse in the partial breast radiotherapy group, which suggests that dose-time effects were the dominant factor over reduced irradiated volume within this study. Other randomised trials using similar dose-fractionation regimens to RAPID have yet to publish mature outcome data although early reports suggest limited toxicity.

A second novel aspect is the engagement of patients to produce the most comprehensive patient reported outcomes in any published partial breast radiotherapy trial to date. It is obvious that the patient's viewpoint is extremely important, but previous breast radiotherapy trials have also demonstrated that patient reported outcomes are very sensitive in distinguishing between different dose-fractionation regimens [25]. IMPORT LOW suggests that patient reported outcomes are also able to detect a radiotherapy volume effect. This observation is highly relevant for the design of future breast radiotherapy trials as patient reported outcomes could prove to be the most cost-effective yet sensitive and patient-centred method of outcome assessment. We have analysed and presented the late normal tissue toxicity for both patient reported outcomes and clinician reported outcomes in two ways: using discrete 5 year time points and also the cumulative incidence. The purpose of dual analysis is to convey different information, in that the longitudinal results capture the maximum grades of toxicity, whereas the cross sectional 5 year results take into account resolution of some side effects, such as oedema that may reduce over time. We acknowledge that multiple statistical tests were conducted for the normal tissue toxicity analysis, but we accounted for this by using a stringent significance level of 0.005 for clinical and patient reported outcomes.

A third important strength of IMPORT LOW is its simplicity. The partial breast radiotherapy technique uses standard tangential fields that are simply shortened to encompass the tumour bed and margin of healthy tissue. This means that a larger volume of breast is treated in comparison with other 3D conformal/IMRT and brachytherapy techniques, but tangential beams minimise dose to surrounding organs at risk such as the heart and lungs by keeping the exit

beams within the breast. This may be important in minimising second radiation-induced cancers. It may also minimise the mean heart dose without the need for breath-hold in most left-sided breast cancer patients, given that the majority of patients have tumours in the upper half of the breast and above the level of the heart [26] [[27]. The tangential field arrangement is more likely to deliver at least some dose to the lower axilla in comparison with more conformal partial breast radiotherapy techniques. This may prove to be important in minimising axillary recurrences [28]. A simple form of forward planned IMRT was used to optimise dose homogeneity, but this is now standard in the vast majority of centres [29, 30]. This means that implementation of this technique does not require additional resources or training in the majority of countries.

By today's standards, the original estimates of local relapse rate on which sample size was based were high given recent improvements in outcome [11]. Retrospective power calculations, based on year 5 data being available for 1832 (91%) patients and an observed control group local relapse rate of 1.1%, confirm that a clinically relevant absolute 2.0% increase in 5-year local relapse rate could be excluded for each test group, assuming 80% power and 2.5% alpha (one-sided). The demonstration of non-inferiority is expected to be stable with increasing follow-up, although the local relapse rate in IMPORT LOW is likely to be in the range 1-3% by 10 years. This expectation is based on the ELIOT trial in which the cumulative incidence of local relapse in the intra-operative group rose in an apparently linear fashion between 5 and 9 years [23]. Compliance with photographic assessments was not as high as anticipated. However, given the relatively low rate of any change in breast appearance at 5 years in the control group (23%), retrospective power calculations indicate that there would be 75% power to detect a difference of 10% (with a 2.5% significance level).

Another possible limitation is bias in late normal tissue toxicity reporting as it is impossible to blind patients and clinicians to treatment randomisation. The panel of assessors undertaking photographic assessments are however blinded to treatment arm, albeit that photographic assessments appear less sensitive to subtle changes in normal-tissue toxicity.

A major question raised by this trial is: which patients should be selected for partial breast radiotherapy? IMPORT LOW had relatively permissive eligibility criteria, but it is apparent from the baseline characteristics that the majority of women actually recruited had small, low grade, ER+, node negative tumours. This may be partly explained by the widening of eligibility criteria during recruitment. Appendix 3 shows that despite the proportional lower number of patients with higher risk disease, this group contributed 8 out of 18 of the local relapses. However, this observation needs to be taken with caution as the overall number of events was very low. The UK has taken a pragmatic approach to patient selection for partial breast radiotherapy by producing a consensus statement ([breast-cancer-uk-consensus-statements](#)), which states that

partial breast radiotherapy can be considered for patients ≥ 50 years, grade 1–2, ≤ 30 mm, ER+, HER2-, N0 with minimum 1 mm radial excision margins for invasive disease. Given the very small percentage of node positive patients in IMPORT Low, we support the UK Breast Radiotherapy Consensus in not recommending partial breast radiotherapy for this group. Consistent with the findings of ACOSOG Z0011, IBSCG 23-01, NCIC MA20, and EORTC 22922, we recommend that node positive patients receive whole breast radiotherapy as standard of care.

A further controversy raised by this and other reported studies, is the definition of ipsilateral “local relapse”. For example the IMPORT LOW definition is recurrence of *any* pre-invasive/invasive carcinoma in the ipsilateral breast regardless of histology or location of the index breast cancer. The GEC-ESTRO trial definition does not take into account location within the breast, but does exclude tumours with differing histology and the Cochrane review only includes relapses within the index quadrant with the same histology. Clearly, inclusion or exclusion of local relapses could make a substantial difference in reported results given the very low event rate in this patient group.

Finally, the results of IMPORT LOW are not consistent with the 2016 overview by the Cochrane Collaboration based on the published data of phase III trials, 6 of which contributed to analyses of local relapses and 4 to analyses of toxicity endpoints [31]. This overview reported inferior results for both local relapse and late normal tissue toxicity with partial breast radiotherapy. The relatively small number of contemporary partial breast radiotherapy trials included within this report may explain these findings [30]. Four other phase II trials testing partial breast radiotherapy are yet to report 5-year results: NSAPBP/RTOG, RAPID, SHARE and IRMA. The mature results from over 10,000 patients recruited within these important trials will add to the literature in due course.

It is clear that we need the results from as yet unpublished partial breast radiotherapy trials, but due to the huge heterogeneity in dose-fractionation regimen, radiotherapy technique, irradiated volume and inconsistencies in definition of ipsilateral breast tumour recurrence, it may prove challenging to interpret these data. A large individual patient data meta-analysis may go some way to resolving this potential dilemma and we strongly support this initiative.

We also recognise the importance of investigating possible effects of partial breast radiotherapy on development of radiation induced second cancer and major cardiac events. However, this research will require thousands of patients followed up for many years before robust conclusions can be made and may be best achieved by future interrogation of routine health data.

Another approach will be to investigate the biology of local relapse and its relationship to partial breast radiotherapy. For example, it is still unclear what constitutes a “true” ipsilateral recurrence from an ipsilateral new primary at the molecular level and this requires further investigation.

Conclusion

At 5 years, partial breast radiotherapy delivered using a simple intensity modulated technique achieved non-inferiority in local relapse rates compared with whole breast radiotherapy and comparable or reduced late adverse effects. This method of partial breast radiotherapy appears safe and effective and could be implemented easily within the majority of radiotherapy centres worldwide.

Declaration of interests

We declare we have no conflicts of interest.

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The IMPORT Trialists’ Group consists of the Trial Management Group, Trial Steering Committee, Independent Data Monitoring Committee and the principal and main co-investigators at the participating centres.

IMPORT LOW is sponsored by The Institute of Cancer Research, London.

Contributors

CEC and JRY are the current and previous chief investigators. AK is the chief clinical coordinator. JMB is the scientific lead for the study within the Institute of Cancer Research Clinical Trials and Statistics Unit and provided oversight and guidance for trial management and statistical analysis throughout. JYR, JMB, CEC and JSH were responsible for the study design. JMB, CEC, JRY, AK and CG were responsible for data interpretation and writing the report. CG and JH undertook the statistical analysis. ME, JT, RK and IB managed the study and data collection. MW and MJ are patient advocate members of the trial management group and provided guidance for study documentation and reports. YT and LC were the quality assurance radiographer and physicist and contributed to radiotherapy planning and quality assurance. ED was involved in radiotherapy planning and set up. RA, AA, MB, CC, AH, ES, IS and DW are principal investigators (past or present) at participating centres and members of the trial management group and were responsible for patient recruitment and contributed to the report through review and discussion. PH is the Patient Reported Outcomes lead. All authors reviewed the manuscript.

Research in context

Evidence before this study

A comprehensive literature search using PubMed and Medline was carried out before the trial opened and addressed the following (i) identification of all previous pathological and clinical breast radiotherapy studies investigating patterns of recurrence within the ipsilateral breast and (ii) results of previous partial breast radiotherapy studies. We concluded that existing research suggested that the majority of local relapses occur in the vicinity of the original tumour bed and that older trials testing partial breast radiotherapy were uninformative due to suboptimal patient selection, poor localisation of the tumour and, hence, inaccurate radiotherapy. We hypothesised that partial breast radiotherapy using modern methods of radiotherapy planning and treatment would be non-inferior in terms of local relapse rates and may have reduced normal tissue toxicity in a low risk of relapse population. This formed part of our peer-reviewed funding application for the trial.

Added value of this study

IMPORT LOW is the first phase III trial reporting 5-year outcome data for local relapse and adverse effects after partial breast radiotherapy delivered using standard external beam radiotherapy techniques, and is the *only* trial testing the importance of treatment volume

unconfounded by radiotherapy dose-time factors. In addition, it is unique by including very comprehensive patient reported outcome measures.

At 5 years, partial breast radiotherapy delivered using a simple and standard technique, showed no increase in local relapse rates compared with whole breast radiotherapy, and produced equivalent or reduced late adverse effects. Follow-up is continuing and 10 year local relapse rates and toxicity will be reported.

Implications of all the available evidence

IMPORT LOW has similar local relapse rates compared with the recently reported GEC-ESTRO brachytherapy partial breast radiotherapy trial that also confirmed non-inferiority. Our method of partial breast radiotherapy appears safe and effective and a key advantage of the IMPORT LOW partial breast technique is its relative simplicity compared with conformal/inverse planned intensity modulated radiotherapy or brachytherapy. The use of standard medial and lateral tangential beams also minimise the mean heart dose without the need for breath hold in most left-sided breast cancer patients, given that the majority of patients have tumours in the upper half of the breast and above the level of the heart. Implementation of this technique will not require additional resources or training in the majority of countries worldwide.

Figure legends

Figure 1 – Radiotherapy technique for partial breast group

Figure 2 - CONSORT Flow Chart

Figure 3 - Cumulative hazard of local relapse by treatment group

Figure 1: Radiotherapy technique for partial breast group. Red denotes the partial breast planning target volume and blue shows the radiotherapy field arrangements shaped with multileaf collimators. See planning pack, appendix 2, for further details.

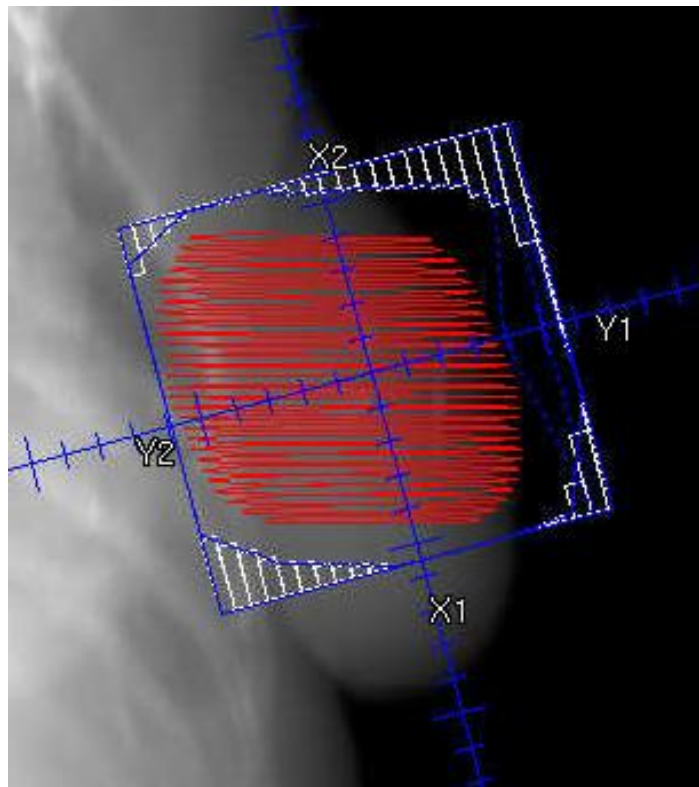


Figure 2 - CONSORT Flow Chart

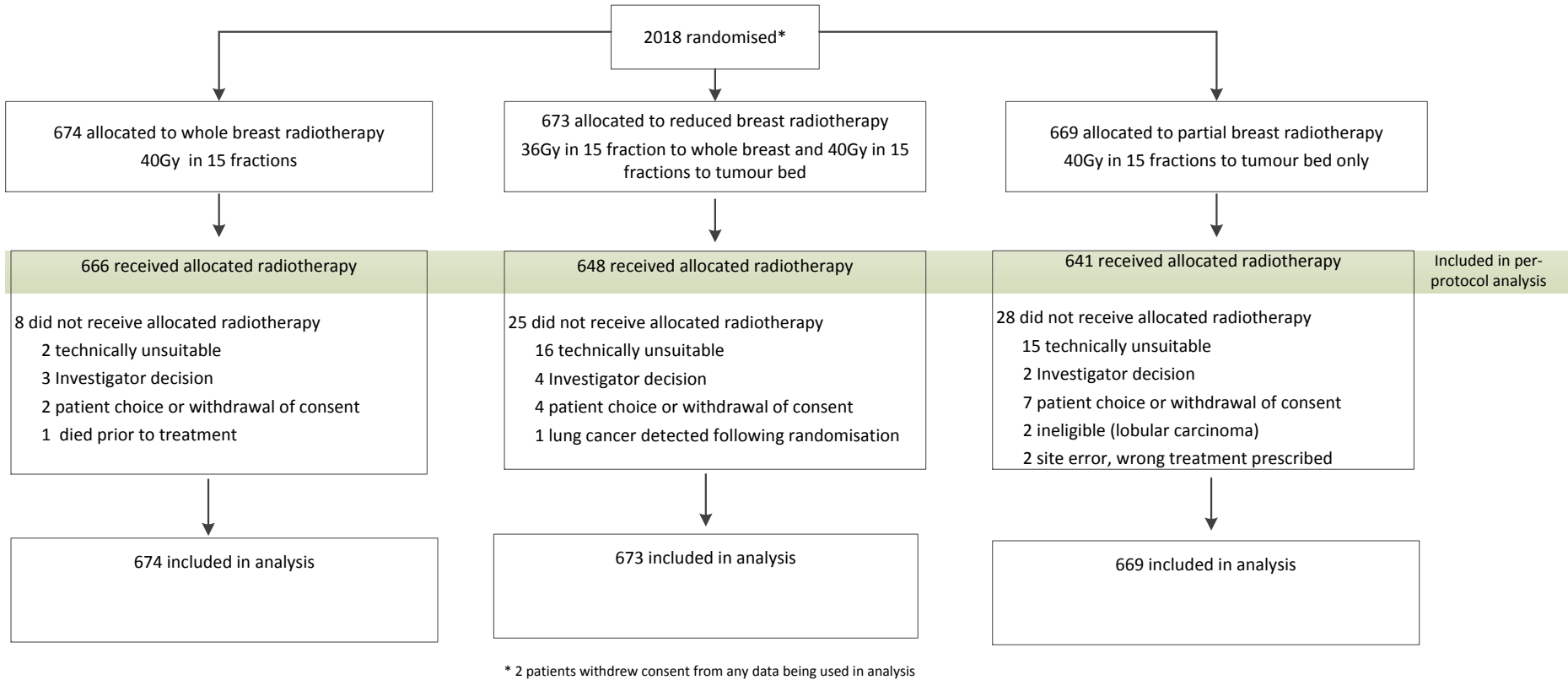
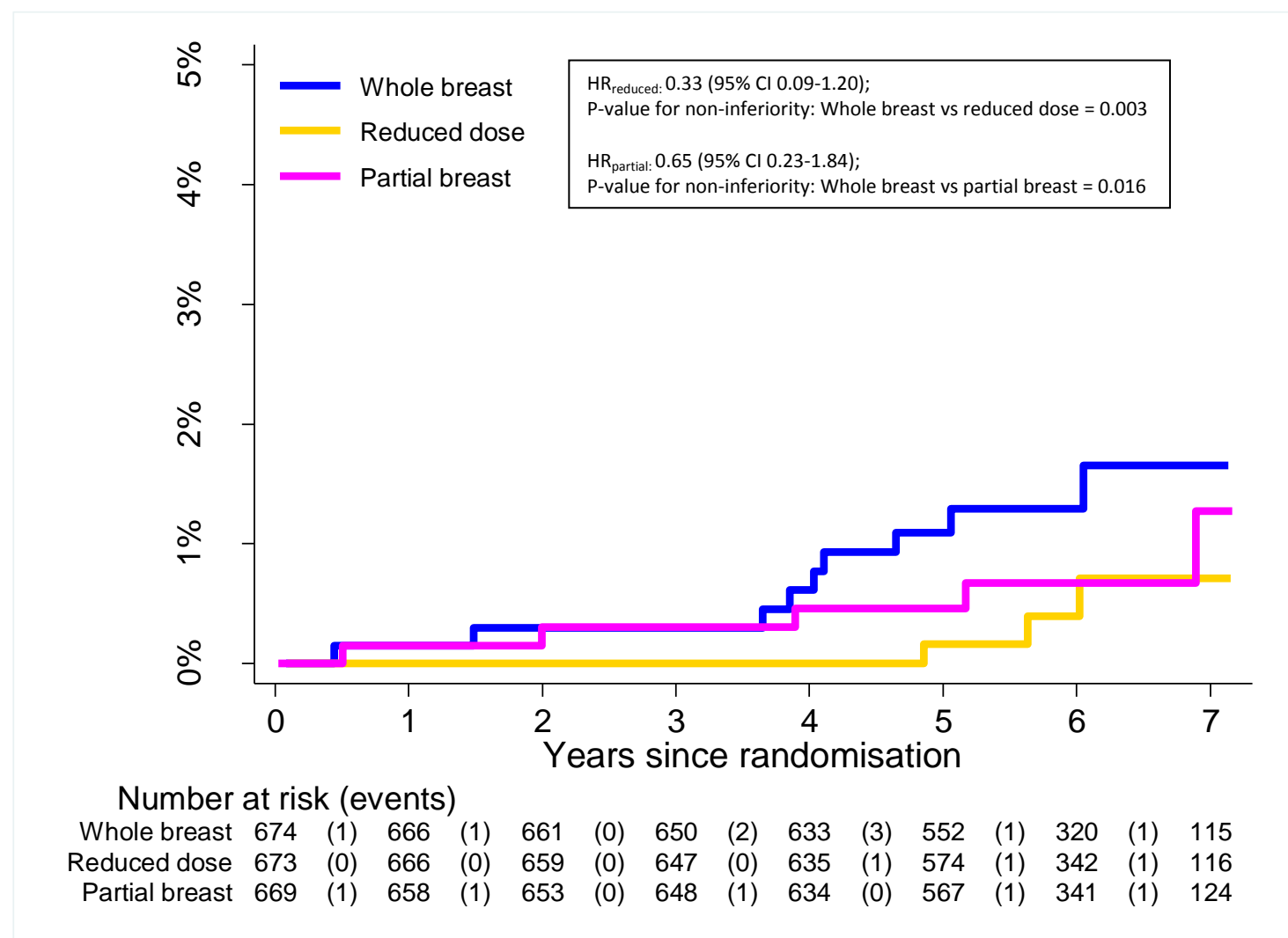


Figure 3 Cumulative hazard of local relapse by treatment group



Tables

Table 1 Demographic and clinical characteristics at randomisation by treatment group (n=2016*)

		Whole breast	Reduced dose	Partial breast
		N=674 N (%)	N=673 N (%)	N=669 N (%)
Age	Median (IQR)	62 (57-67)	63 (57-67)	62 (57-67)
Side of primary	Left	336 (50)	344 (51)	348 (52)
	Right	338 (50)	329 (49)	321 (48)
	Not known	0	0	0
Pathological tumour size (cm)	Median (IQR)	1.2 (0.8-1.5)	1.1 (0.8-1.6)	1.2 (0.8-1.6)
	Not known	0	0	1
Tumour grade	1	298 (45)	272 (40)	284 (43)
	2	310 (46)	328 (49)	320 (48)
	3	64 (9)	73 (11)	63 (9)
	Ungradeable	2	0	1
	Not known	0	0	0
Re-excision	Yes	93 (14)	78 (12)	87 (13)
	No	580 (86)	595 (88)	580 (87)
	Not known	1	0	2
Axillary surgery performed	Yes	672 (99)	673 (100)	666 (99)
	No	1 (<1)	0	1 (<1)
	Not known	1	0	2
Pathological node status	Positive	24 (4)	19 (3)	16 (2)
	Negative	650 (96)	654 (97)	653 (98)
	Not known	0	0	0
Histological type	Infiltrating ductal	578 (86)	581 (86)	563 (85)
	Mixed	14 (2)	18 (3)	22 (3)
	Other	79 (12)	73 (11)	80 (12)
	Not known	3	1	4
Lymphovascular invasion	Present	34 (7)	47 (10)	35 (7)
	Absent	459 (93)	445 (90)	459 (93)
	Not known	181	181	175
ER status	Positive	640 (95)	638 (95)	633 (95)
	Poor [†]	32 (5)	34 (5)	34 (5)
	Not known	2	1	2
PR status	Positive	400 (81)	393 (82)	380 (80)
	Poor [†]	93 (19)	84 (18)	95 (20)
	Not known	181	196	194

HER2 status	Negative	599 (96)	603 (96)	580 (94)
	Positive	23 (4)	25 (4)	34 (6)
	Not known	52	45	55
Adjuvant therapy received (not mutually exclusive)	Chemotherapy	29 (4)	42 (6)	33 (5)
	Endocrine therapy	610 (91)	614 (91)	602 (90)
	Trastuzumab	7 (1)	15 (2)	14 (2)
	Not known	1	3	4

* Two patients withdrew consent for any of their data to be used in analysis

†ER/PR poor refers to less than 10% receptor staining

Table 2 Relapse and mortality by treatment group

	Cumulative no. of events	Cumulative incidence by 5 years	Hazard ratio ¹ (95% CI)	p-value ²
	n / pts (%)			
Local relapse				
Whole breast	9/674 (1)	1.1 (0.5-2.3)	1	-
Reduced dose	3/673 (1)	0.2 (0.02-1.2)	0.33 (0.09-1.20)	0.077
Partial breast	6/669 (1)	0.5 (0.2-1.4)	0.65 (0.23-1.84)	0.420
Local-regional relapse				
Whole breast	9/674 (1)	1.1 (0.5-2.3)	1	
Reduced dose	3/673 (1)	0.2 (0.02-1.2)	0.33 (0.09-1.21)	0.077
Partial breast	8/669 (1)	0.8 (0.3-1.8)	0.88 (0.34-2.27)	0.761
Distant relapse				
Whole breast	13/674 (2)	1.4 (0.7-2.6)	1	
Reduced dose	10/673 (2)	1.5 (0.8-2.8)	0.77 (0.34-1.75)	0.525
Partial breast	12/669 (2)	1.6 (0.8-2.9)	0.92 (0.42-2.03)	0.838
Any breast cancer-related event				
Whole breast	33/674 (5)	3.7 (2.5-5.4)	1	
Reduced dose	24/673 (4)	3.4 (2.2-5.1)	0.72 (0.43-1.22)	0.223
Partial breast	33/669 (5)	4.0 (2.8-5.9)	1.00 (0.62-1.62)	0.982
All-cause mortality				
Whole breast	40/674 (6)	5.0 (3.6-7.0)	1	
Reduced dose	39/673 (6)	4.1 (2.8-5.9)	0.97 (0.62-1.50)	0.883
Partial breast	37/669 (6)	3.7 (2.5-5.4)	0.91 (0.58-1.42)	0.693

¹ Hazard ratio <1 favours experimental group

² Log-rank test, for each experimental group compared with whole breast radiotherapy

Table 3- Local relapse, second cancers and deaths by treatment group

	Whole breast N=674 N (%)	Reduced dose N=673 N (%)	Partial breast N=669 N (%)	Total N=2016 N (%)
Local relapse	9¹ (1)	3² (1)	6 (1)	18 (1)
<i>Local relapse within radiotherapy field</i>				
Yes	9	1	4	14
No	0	0	0	0
Borderline	0	0	1	1
Not documented	0	2	1	3
Contralateral breast second primary	12 (2)	13 (2)	13 (2)	38 (2)
Invasive	10	11	11	32
DCIS	2	2	2	6
Non-breast second primary	35 (5)	37 (5)	24 (3)	96 (5)
Colorectal	10 ³	7	3	20
Lung	11 ³	4	4	19
Gynaecological	5	8	4	17
Other ⁴	4	3	1	8
Oesophagus	0	3	3	6
Pancreas	1	2	3	6
Lymphoma	0	2	3	5
Genitourinary	3	1	0	4
Head & neck	1	2	0	3
Liver	0	2	1	3
Cancer of unknown primary	0	0	2	2
Peritoneal	0	2	0	2
Sarcoma	1	1 ⁵	0	2
Deaths	40 (6)	39 (6)	37 (6)	116 (6)
Cause of death:				
Breast cancer	9 ⁶	7 ⁷	10 ⁸	26
Second cancer	14	16	12	42
Cardiac	5	2	2	9
Other – cerebrovascular accident	1	2	1	4
Other – pulmonary embolism	0	2	0	2
Other	11	10	10	31
Unknown	0	0	2	2

¹ Two patients with DCIS

² One patient with DCIS

³ One patient reported a colorectal second cancer followed by a lung second cancer and is included as both categories

⁴ Other includes adrenal, squamous cell carcinoma of the skin, melanoma, leukaemia and mesothelioma

⁵ Angiosarcoma developed in the treated breast

⁶ One patient with distant relapse prior to death died from mesothelioma

⁷ One patient with distant relapse prior to death died from renal failure

⁸ Two patients with distant relapse prior to death also died from other causes, one sepsis and one was cardiac related

Table 4 Patient assessments of moderate/marked late adverse events

Moderate/marked events	Cumulative no. of events	Cumulative incidence by 5 ¹ years	Hazard ratio (95% CI) p-value ²	Proportion with event at 5 years	p-value ³
	n / pts randomised (%)		Comparison with whole	n / pts (%)	Comparison with whole
Breast appearance changed					
whole	158/411 (38)	47.7 (41.1-54.8)	1	80/295 (27)	
reduced	123/433 (28)	36.7 (30.6-43.6)	0.74 (0.54-1.00), p=0.051	66/325 (20)	0.047
partial	113/421 (27)	35.1 (28.7-42.5)	0.64 (0.46-0.89), p=0.007	49/331 (15)	<0.0001
Breast smaller					
whole	119/411 (29)	37.3 (30.9-44.4)	1	66/294 (23)	
reduced	110/433 (25)	31.9 (26.3-38.4)	0.83 (0.59-1.16), p=0.280	63/326 (19)	0.373
partial	104/421 (25)	34.7 (27.5-43.0)	0.78 (0.54-1.11), p=0.162	56/331 (17)	0.086
Breast harder/firmer					
whole	115/411 (28)	35.3 (28.4-43.3)	1	27/292 (9)	
Reduced	74/433 (17)	21.0 (16.2-26.9)	0.53 (0.36-0.79), p=0.002	23/325 (7)	0.376
partial	58/421 (14)	15.3 (12.0-19.5)	0.47 (0.32-0.71), p<0.0001	15/330 (5)	0.024
Arm/shoulder pain					
whole	98/411 (24)	32.6 (26.3-39.9)	1	33/297 (11)	
reduced	104/433 (24)	30.1 (24.7-36.4)	0.94 (0.71-1.25), p=0.678	43/329 (13)	0.465
partial	97/421 (23)	27.2 (21.9-33.6)	0.97 (0.73-1.28), p=0.809	24/331 (7)	0.097
Swollen arm/hand					
whole	21/411 (5)	6.2 (4.1-9.5)	1	5/295 (2)	
reduced	26/433 (6)	9.8 (6.2-15.3)	1.19 (0.67-2.11), p=0.558	15/330 (5)	0.066
partial	16/421 (4)	4.4 (2.7-7.3)	0.59 (0.30-1.15), p=0.123	2/330 (1)	0.264
Difficulty raising arm					
whole	42/411 (10)	13.6 (9.2-19.8)	1	10/297 (3)	
reduced	45/433 (10)	14.0 (9.8-19.8)	0.98 (0.64-1.50), p=0.913	17/328 (5)	0.326
partial	47/421 (11)	13.5 (10.1-18.0)	1.08 (0.71-1.64), p=0.726	15/331 (5)	0.542
Shoulder stiffness					
whole	56/411 (14)	19.3 (14.0-26.5)	1	12/296 (4)	
Reduced	56/433 (13)	19.3 (13.9-26.4)	0.93 (0.64-1.35), p=0.701	22/328 (7)	0.161
partial	58/421 (14)	15.3 (12.0-19.5)	1.06 (0.73-1.54), p=0.756	13/331 (4)	0.999
Breast pain					

	whole	67/411 (16)	19.1 (14.9-24.3)	1	13/295 (4)	
	reduced	65/433 (15)	16.9 (12.9-22.1)	0.96 (0.68-1.35), p=0.812	18/330 (5)	0.584
	partial	64/421 (15)	18.2 (14.1-23.4)	0.96 (0.68-1.36), p=0.830	13/328 (4)	0.842
Breast swollen	whole	31/411 (8)	8.1 (5.7-11.3)	1	1/295 (<1)	
	reduced	26/433 (6)	6.8 (4.7-9.9)	0.84 (0.49-1.41), p=0.503	4/329 (1)	0.377
	partial	17/421 (4)	4.7 (2.9-7.6)	0.49 (0.27-0.89), p=0.019	1/328 (<1)	0.999
Breast oversensitive	whole	64/411 (16)	17.2 (13.7-21.5)	1	9/296 (3)	
	reduced	59/433 (14)	16.5 (12.0-22.4)	0.89 (0.62-1.27), p=0.526	16/330 (5)	0.308
	partial	54/421 (13)	18.3 (13.0-25.5)	0.80 (0.55-1.14), p=0.220	13/330 (4)	0.665
Skin problems in breast	whole	50/411 (12)	15.7 (11.1-21.9)	1	7/296 (2)	
	reduced	42/433 (10)	13.4 (9.2-19.2)	0.78 (0.52-1.18), p=0.237	10/328 (3)	0.632
	partial	35/421 (9)	9.2 (6.7-12.7)	0.64 (0.42-0.99), p=0.045	9/330 (3)	0.806
Skin appearance changed	whole	63/411 (15)	21.0 (15.5-27.9)	1	22/294 (8)	
	reduced	59/433 (14)	17.9 (13.2-24.0)	1.07 (0.68-1.68), p=0.775	23/325 (7)	0.878
	partial	49/421 (12)	14.6 (10.4-20.5)	0.87 (0.54-1.40), p=0.569	12/330 (4)	0.051

¹ Estimated at 5 years and 3 months; ² Wald test; ³ Fisher's Exact test

Table 5 Clinician assessment of moderate/marked late adverse events

Moderate/marked events	Cumulative no. of events	Cumulative incidence by 5 ¹ years	Hazard ratio (95% CI) p-value ²	Proportion with event at 5 years	p-value ³
	n / pts randomised (%)		Comparison with whole	n / pts (%)	Comparison with whole
Worst NTE					
whole	134/674 (20)	27.6 (22.5-33.6)	1	60/457 (13)	
reduced	108/673 (16)	21.1 (17.2-25.7)	0.77 (0.60-0.99), p=0.043	48/480 (10)	0.152
partial	94/669 (14)	20.0 (15.6-25.4)	0.69 (0.53-0.90), p=0.006	49/474 (10)	0.221
Breast shrinkage					
whole	79/674 (12)	18.4 (13.7-24.5)	1	41/452 (9)	
reduced	70/673 (10)	13.6 (10.6-17.5)	0.86 (0.62-1.18), p=0.345	37/478 (8)	0.480
partial	61/669 (9)	13.9 (10.1-19.0)	0.78 (0.56-1.08), p=0.134	33/472 (7)	0.276
Breast induration (index)					
whole	63/674 (9)	12.7 (9.5-16.8)	1	21/453 (5)	
reduced	43/673 (6)	8.4 (6.0-11.6)	0.66 (0.45-0.98), p=0.040	13/474 (3)	0.161
partial	48/669 (7)	10.8 (7.7-15.1)	0.77 (0.53-1.12), p=0.165	24/471 (5)	0.762
Breast induration (outside index)					
whole	15/674 (2)	2.3 (1.4-3.8)	1	2/450 (<1)	
reduced	10/673 (2)	2.1 (1.0-4.1)	0.66 (0.30-1.48), p=0.310	2/464 (<1)	>0.999
partial	-	-	-	-	-
Telangiectasia					
whole	8/674 (1)	1.6 (0.8-3.3)	1	3/445 (1)	
reduced	8/673 (1)	3.0 (1.3-6.8)	0.96 (0.36-2.57), p=0.976	6/468 (1)	0.507
partial	5/669 (1)	0.6 (0.2-1.7)	0.62 (0.21-1.92), p=0.401	4/465 (1)	>0.999
Breast oedema					
whole	24/674 (4)	4.0 (2.6-6.2)	1	4/446 (1)	
reduced	18/673 (3)	3.2 (2.0-5.3)	0.74 (0.40-1.37), p=0.338	2/468 (<1)	0.441
partial	11/669 (2)	1.7 (0.9-3.0)	0.46 (0.23-0.94), p=0.029	0/468 (0)	0.056
Other radiotherapy related					
whole	11/674 (2)	1.7 (1.0-3.1)	1	3/457 (<1)	
reduced	9/673 (1)	1.4 (0.7-2.6)	0.81 (0.34-1.97), p=0.646	0/480 (0)	0.263
partial	6/669 (1)	0.9 (0.4-2.0)	0.55 (0.20-1.49), p=0.234	0/474 (0)	0.221

¹ Estimated at 5 years and 3 months; ² Log-rank test; ³ Fisher's Exact test

References

1. Darby, S., et al., *Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials*. Lancet, 2011. **378**(9804): p. 1707-16.
2. Committee, S., *Breast radiotherapy after breast-conserving surgery. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists*. CMAJ, 1998. **158 Suppl 3**: p. S35-42.
3. Sedlmayer, F., et al., *DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer*. Strahlenther Onkol, 2013. **189**(10): p. 825-33.
4. Belkacemi, Y., et al., *Patterns of practice of regional nodal irradiation in breast cancer: results of the European Organization for Research and Treatment of Cancer (EORTC) Nodal Radiotherapy (NORA) survey*. Ann Oncol, 2015. **26**(3): p. 529-35.
5. Dundas, K.L., et al., *Australian survey on current practices for breast radiotherapy*. J Med Imaging Radiat Oncol, 2015. **59**(6): p. 736-42.
6. Smith, B.D., et al., *Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO)*. Int J Radiat Oncol Biol Phys, 2009. **74**(4): p. 987-1001.
7. Polgar, C., et al., *Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study*. Radiother Oncol, 2010. **94**(3): p. 274-9.
8. Polgar, C., et al., *Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)*. Radiother Oncol, 2010. **94**(3): p. 264-73.
9. Wilkinson, J.B., et al., *Evaluation of current consensus statement recommendations for accelerated partial breast irradiation: a pooled analysis of William Beaumont Hospital and American Society of Breast Surgeon MammoSite Registry Trial Data*. Int J Radiat Oncol Biol Phys, 2013. **85**(5): p. 1179-85.
10. Shah, C., et al., *The American Brachytherapy Society consensus statement for accelerated partial breast irradiation*. Brachytherapy, 2013. **12**(4): p. 267-77.
11. Mannino, M. and J.R. Yarnold, *Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld?* Radiother Oncol, 2009. **90**(1): p. 14-22.
12. Salvadori, B., et al., *Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery*. Br J Surg, 1999. **86**(1): p. 84-7.
13. Coles, C.E., et al., *Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery: audit on behalf of the IMPORT Trial Management Group*. Eur J Surg Oncol, 2009. **35**(6): p. 578-82.
14. Harris, E.J., et al., *Characterization of target volume changes during breast radiotherapy using implanted fiducial markers and portal imaging*. Int J Radiat Oncol Biol Phys, 2009. **73**(3): p. 958-66.
15. Coles, C.E., et al., *Intensity-modulated Radiotherapy for the Treatment of Breast Cancer*. Clin Oncol (R Coll Radiol), 2013. **25**(3): p. 215.
16. Theberge, V., et al., *Altered fractionation: rationale and justification for whole and partial breast hypofractionated radiotherapy*. Semin Radiat Oncol, 2011. **21**(1): p. 55-65.
17. Marta, G.N., et al., *Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials*. Radiother Oncol, 2015. **114**(1): p. 42-9.
18. Strnad, V., et al., *5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial*. Lancet, 2016. **387**(10015): p. 229-38.

19. Yarnold, J. and C. Coles, *Trial Protocol, version 4, 19.02.2008. On behalf of the IMPORT LOW Trial Management Group: Intensity Modulated and Partial Organ Radiotherapy. Randomised trial testing intensity modulated and partial organ radiotherapy following breast conservation surgery for early breast cancer.* 2008, The Institute of Cancer Research: Royal Cancer Hospital: Sutton, Surrey, UK. p. 1-74.
20. Schaverien, M.V., et al., *Use of boost radiotherapy in oncoplastic breast-conserving surgery - a systematic review.* Eur J Surg Oncol, 2013. **39**(11): p. 1179-85.
21. Yarnold, J., et al., *Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial.* Radiother Oncol, 2005. **75**(1): p. 9-17.
22. Haviland, J.S., et al., *Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer.* Clin Oncol (R Coll Radiol), 2008. **20**(7): p. 497-501.
23. Veronesi, U., et al., *Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial.* Lancet Oncol, 2013. **14**(13): p. 1269-77.
24. Livi, L., et al., *Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial.* Eur J Cancer, 2015. **51**(4): p. 451-63.
25. Haviland, J.S., et al., *Do Patient-reported Outcome Measures Agree with Clinical and Photographic Assessments of Normal Tissue Effects after Breast Radiotherapy? The Experience of the Standardisation of Breast Radiotherapy (START) Trials in Early Breast Cancer.* Clin Oncol (R Coll Radiol), 2016. **28**(6): p. 345-53.
26. Donovan, E.M., et al., *Second cancer incidence risk estimates using BEIR VII models for standard and complex external beam radiotherapy for early breast cancer.* Med Phys, 2012. **39**(10): p. 5814-24.
27. Kirby, A.M., et al., *Prone versus supine positioning for whole and partial-breast radiotherapy: a comparison of non-target tissue dosimetry.* Radiother Oncol, 2010. **96**(2): p. 178-84.
28. Gentilini O, B.E., Leonardi MC, Rotmensz N, Vila J, Peradze N, Thomazini MV, Jereczek BA, Galimberti V, Luini A, Veronesi P, Orecchia R., *ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy.* Radiother Oncol. , 2017.
29. Mukesh, M.B., et al., *Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis.* J Clin Oncol, 2013. **31**(36): p. 4488-95.
30. Vaidya, J.S., et al., *Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial.* Lancet, 2014. **383**: p. 603-13.
31. Hickey, B.E., et al., *Partial breast irradiation for early breast cancer.* Cochrane Database Syst Rev, 2016. **7**: p. CD007077.